REVOLUTION Medicines Announces First Patient Dosed with RMC-4630 in Phase 1 Clinical Study in Patients with Advanced Solid Tumors

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-- Scientific publication reports preclinical results showing precision oncology opportunity for targeting SHP2 in genetically selected tumors --

REDWOOD CITY, Calif.--(BUSINESS WIRE)--REVOLUTION Medicines, Inc. today announced dosing of the first patient in a Phase 1, open-label, monotherapy dose-escalation and expansion study of RMC-4630, the company's lead investigational drug candidate targeting the enzyme SHP2. REVOLUTION Medicines holds the IND for RMC-4630, and this trial is being conducted under the recently announced global partnership on SHP2 between REVOLUTION Medicines and Sanofi. Initiation of this clinical trial represents an important step in the company's mission to translate frontier oncology targets on behalf of cancer patients.

"REVOLUTION Medicines is proud to advance RMC-4630 into clinical development on behalf of patients with advanced cancers who have limited treatment options," said Stephen Kelsey, M.D., FRCP, FRCPath, president of R&D of REVOLUTION Medicines. "Our discovery of optimal inhibitors of SHP2 and elucidation of the critical role of SHP2 in the growth of certain cancers has, for the first time, suggested the potential to render these drivers of cancer clinically actionable. We are eager to advance this program by working with patients, experienced clinical investigators and our development partners at Sanofi."

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical activity of RMC-4630 in people with relapsed, refractory solid tumors including non-small cell lung cancer and other tumor types carrying certain mutations that cause hyperactivation of the RAS-MAP kinase cell growth signaling cascade. Despite notable recent therapeutic advances in the management of lung cancer and melanoma, there remain large unmet medical needs as no targeted therapies have been approved for treating patients with solid tumors carrying these specific mutations. The study will comprise two parallel components: (1) a dose escalation study for patients with solid tumors, and (2) an expansion study for patients with tumors harboring specific mutations.

Original research led by scientists at REVOLUTION Medicines, and conducted in collaboration with researchers at the University of California, San Francisco School of Medicine, discovered that cancers caused by these oncogenic signaling proteins rely on the normal biochemical actions of SHP2. These data were first disclosed in preliminary form in 2017 via *BioRxiv,* and have now been published in a full peer-reviewed paper in *Nature Cell Biology.* They demonstrated that cancers with such "semi-autonomous" mutations may be susceptible to treatment with an inhibitor of SHP2. The trial of RMC-4630 will explore precision oncology hypotheses based on these findings at several clinical centers, including the University of California, Irvine, Chao Family Comprehensive Cancer Center.

The Role of SHP2 in Cancer

SHP2 (PTPN11), a cellular enzyme in the protein tyrosine phosphatase family, plays an important role in multiple forms of cancer and in anticancer immunity. Recently REVOLUTION Medicines reported discoveries about the regulation by SHP2 of a cell growth signaling pathway, known as the RAS-MAP kinase pathway, that frequently is hyperactive in human cancers. The research showed that some mutated forms of proteins in the RAS-MAP kinase pathway depend on SHP2 for their oncogenic activity, and that small molecule inhibitors of SHP2 designed by the company may reduce their tumorigenic effects.

About RMC-4630

RMC-4630 is a potent, selective and orally administered small molecule inhibitor of SHP2. RMC-4630 acts by stabilizing the SHP2 protein in an inactive conformation that is unable to transmit cell growth signals. RMC-4630 as a single agent was found to attenuate signal transduction through the RAS-MAP kinase cascade, reduce tumor growth and cause tumor cell death in preclinical xenograft studies of human tumors carrying select mutations in the RAS-MAP kinase pathway.

About REVOLUTION Medicines

The mission of REVOLUTION Medicines is to discover and develop new drugs directed toward frontier oncology targets for cancer patients. Frontier targets include proteins that drive the growth and survival of cancer but carry atypical structural or regulatory features requiring unconventional drug discovery strategies. The company bring together deep talent in cancer biology and small molecule drug discovery supported by advanced chemical synthesis, computational and assay technologies to master these targets. Seasoned translational and development scientist help to fulfill the company's commitment to precision oncology.

Headquartered in Redwood City, Calif. at the intersection of Silicon Valley and the birthplace of biotechnology, REVOLUTION Medicines is a private company financed by top-tier investors.

REVOLUTION Medicines: *Translating frontier oncology targets to outsmart cancer* ™

Relevant links:

RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers: Nature Cell Biology

Dose Escalation of RMC-4630 Monotherapy in Relapsed/Refractory Solid Tumors: ClinicalTrials.gov NCT03634982

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